EXHIBIT 5

U 7022948

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

July 27, 2006

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *5,362,755*
ISSUE DATE: *November 08, 1994*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

P. SWAIN
Certifying Officer

US005362755A

United States Patent [19]

Barberich et al.

[11] Patent Number: 5,362,755

[45] Date of Patent: Nov. 8, 1994

[54] METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor, Inc., Marlborough, Mass.

[21] Appl. No.: 163,581

[22] Filed: Dec. 7, 1993

Related U.S. Application Data

[63] Continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[5] A61K 31/135

[52] U.S. Cl. 514/649; 514/826

[58] Field of Search 514/649, 826

[56] References Cited

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Primary Examiner—Raymond J. Henley, III.

Attorney, Agent, or Firm—Hedin & Rothenberg

[57] ABSTRACT

The optically pure R(−) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(−) isomer of albuterol for treating asthma while minimizing the side effects associated with chronic administration of racemic albuterol.

7 Claims, No Drawings

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

This application is a continuation of application Ser. No. 07/896,725 filed Jun. 9, 1992 now abandoned which is a continuation of copending application Ser. No. 07/461,262 filed on Jan. 5, 1990 now abandoned.

DESCRIPTION

1. Background

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent broncho-dilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesis are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1[(-tert-butylamino) methyl]-4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein mean that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline; or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the

optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

Equivalents

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration of racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method of claim 1 wherein the amount of the R(−) isomer of albuterol is greater than approximately 90% by weight of total albuterol.

3. A method of claim 2 wherein the amount of the R(−) isomer of albuterol is greater than 99% by weight of total albuterol.

4. A method of claim 1 comprising administering to the individual by inhalation from approximately 30 mcg to approximately 90 mcg of the R(−) isomer of albuterol per dose.

5. A method of claim 1 comprising orally administering to the individual from approximately 1 mg to approximately 8 mg of the R(−) isomer of albuterol two to four times daily.

6. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration of racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

7. A method of claim 6 wherein the analgesic is selected from the group consisting of: aspirin, acetaminophen and ibuprofen.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

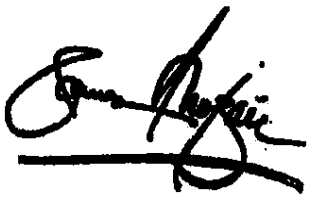
PATENT NO. : 5,362,755
DATED : November 8, 1994
INVENTOR(S) : Barbarich et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 4,
Line 30, delete the word "or" and insert the word -- of --

Signed and Sealed this

Thirtieth Day of September, 2003



JAMES E. ROGAN
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EXHIBIT 6

U 7022945

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July 27, 2006

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *5,547,994*
ISSUE DATE: *August 20, 1996*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

P. SWAIN
Certifying Officer

US005547994A

United States Patent [19]

Barberich et al.

[11] Patent Number: 5,547,994

[45] Date of Patent: Aug. 20, 1996

[54] METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(–) ALBUTEROL

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor, Inc., Marlborough, Mass.

[21] Appl. No.: 335,480

[22] Filed: Nov. 7, 1994

Related U.S. Application Data

[63] Continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[6] A61K 31/135

[52] U.S. Cl. 514/649; 514/826

[58] Field of Search 514/649, 826

[56] References Cited

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Brittain et al. "Some observations on the β-adrenoceptor agonist . . . " *Br. J. Pharmac.* 48, 144–147 (1973).

Hanley et al. "Absolute Configuration of the Optical Isomers of Salbutamol" *J. Med. Chem.* 12, 995 (1971).

Hawkins et al. "Relative Potency of (–)-and (±)-Salbutamol on Guinea Pig . . . " *J. Med. Chem.* 16, 856–857 (1973).

Buckner et al. "Studies on the Effects of Enantiomers of Soterenol, Trimetoquinol . . . " *J. Pharm. Exp. Ther.* 189, 616–625 (1974).

Passowicz-Muszynska E. "Effect on beta adrenergic receptors of tachyphylaxis . . . " *Index Medicus* 91:164287 (1990).

Patwels "Effect of corticosteroids on the action of sympathomimetics" *Index Medicus* 86:051970 (1985).

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Morley et al. "Effects of (+) and racemic salbutamol on airway responses in the guinea pig" *Brit. J. Pharmacol.* 104, 295P (1991).

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Muittari et al. "Comparison of acute bronchodilator effects of oral salbutamol, . . . " *Chem. Abstr.* 89: 123259m (1978).

Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Hedin & Rothenberg, P.C.

[57] ABSTRACT

The optically pure R(–) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(–) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

6 Claims, No Drawings

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(–) ALBUTEROL

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 08/163,581, filed Dec. 7, 1993 and now U.S. Pat. No. 5,362,755, which was a continuation of application Ser. No. 07/896,725, filed Jun. 9, 1992, now abandoned, which was a continuation of application Ser. No. 07/461,262 filed Jan. 5, 1990, now abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(–) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(–) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(–) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(–) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(–) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1 [(tert-butylamino) methyl] -4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(–) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(–) isomer of albuterol is administered to an individual who has asthma. For example, R(–) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(–) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(–) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(–) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(–) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(–) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(–) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a par-

ticular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(–) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(–) isomer may reduce the teratogenic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention

described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of treating an acute attack of asthma, while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to an individual suffering from an acute attack of asthma a quantity of an optically pure R(–) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method of claim 1 wherein the amount of the R(–) isomer of albuterol is greater than approximately 90% by weight.

3. A method of claim 2 wherein the amount of the R(–) isomer of albuterol is greater than 99% by weight.

4. A method of claim 1 comprising administering to the individual by inhalation from approximately 30 mcg to approximately 90 mcg of the R(–) isomer of albuterol per dose.

5. A method of treating an acute attack of asthma, while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to an individual suffering from an acute attack of asthma a quantity of an optically pure R(–) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

6. A method of claim 5 wherein the analgesic is selected from the group consisting of: aspirin, acetaminophen and ibuprofen.

* * * * *

EXHIBIT 7

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

July 27, 2006

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *5,760,090*
ISSUE DATE: *June 02, 1998*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

P. SWAIN
Certifying Officer

US005760090A

United States Patent [19]

Barberich et al.

[11] Patent Number: 5,760,090

[45] Date of Patent: *Jun. 2, 1998

[54] METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor, Inc., Marlborough, Mass.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,362,755.

[21] Appl. No.: 691,604

[22] Filed: Aug. 15, 1996

Related U.S. Application Data

[63] Continuation of Ser. No. 335,480, Nov. 7, 1994, Pat. No. 5,547,994, which is a continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[6] A61K 31/135

[52] U.S. Cl. 514/649; 514/826

[58] Field of Search 514/649

[56] References Cited

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5,547,994	8/1996	Barberich et al.	514/649

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Brittain et al. "Some observations on the β-adrenoceptor agonist . . . " *Br. J. Pharmac.* 48, 144–147 (1973).

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Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Heslin & Rothenberg, P.C.

[57] ABSTRACT

The optically pure R(-) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(-) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

9 Claims, No Drawings

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(−) ALBUTEROL

This is a continuation of U.S. application Ser. No. 08/335,480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547,994, which is a continuation of U.S. application Ser. No. 08/163,581 filed Dec. 7, 1993, now U.S. Pat. No. 5,362,755, which is a continuation of U.S. application Ser. No. 07/896,725, filed Jun. 9, 1992, abandoned, which is a continuation of U.S. application Ser. No. 07/461,262, filed Jan. 5, 1990, abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the broncho-dilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1[(tert-butylamino) methyl]-4-hydroxy-m-xylene-α, α-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc., or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalant form can include, in addition to the drug(s), a liquid carrier and/or

propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of treating asthma, while reducing side effects associated with the administration of racemic albuterol, comprising administering to an individual suffering from asthma a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method according to claim 1, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

3. A method according to claim 1, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim 1, wherein the optically pure R(−) albuterol is administered by inhalation.

5. A method according to claim 4, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

6. A method according to claim 1, wherein the optically pure R(−) albuterol is administered orally.

7. A method according to claim 6, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

8. A method according to claim 6, wherein the optically pure R(−) albuterol is administered as a syrup.

9. A method according to claim 7, wherein the optically pure R(−) albuterol is administered as a syrup.

* * * * *

EXHIBIT 8

U 7022945

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July 27, 2006

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *5,844,002*
ISSUE DATE: *December 01, 1998*

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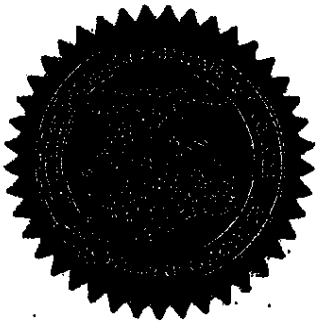
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office



P. SWAIN
Certifying Officer

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United States Patent [19]

Barberich et al.

[11] Patent Number: 5,844,002

[45] Date of Patent: Dec. 1, 1998

[54] METHOD FOR INDUCING BRONCHODILATION USING OPTICALLY PURE R(-) ALBUTEROL

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor, Inc., Marlborough, Mass.

[21] Appl. No.: 63,551

[22] Filed: Apr. 21, 1998

Related U.S. Application Data

[63] Continuation of Ser. No. 691,604, Aug. 15, 1996, Pat. No. 5,760,090, which is a continuation of Ser. No. 335,480, Nov. 7, 1994, Pat. No. 5,547,994, which is a continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[6] A61K 31/135

[52] U.S. Cl. 514/649; 514/826

[58] Field of Search 514/649, 826

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Muittari et al. "Comparison of acute bronchodilator effects of oral salbutamol, . . . " *Chem. Abstr.* 89: 123259m (1978).

Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Heslin & Rothenberg, P.C.

[57] ABSTRACT

The optically pure R(–) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(–) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

10 Claims, No Drawings

METHOD FOR INDUCING BRONCHODILATION USING OPTICALLY PURE R(–) ALBUTEROL

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 08/691,604, filed Aug. 15, 1996, now U.S. Pat. No. 5,760,090, which is a continuation of application Ser. No. 08/335,480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547,994, which is a continuation of application Ser. No. 08/163,581, filed Dec. 7, 1993 now U.S. Pat. No. 5,362,755, which is a continuation of application Ser. No. 07/896,725, filed Jun. 9, 1992 now abandoned, which was a continuation of application Ser. No. 07/461,262, filed Jan. 5, 1990, now abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(–) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs: A composition containing the pure R(–) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the broncho-dilation activity of the R(–) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(–) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(–) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^3[(tert-butylamino) methyl] -4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(–) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(–) isomer of albuterol is administered to an individual who has asthma. For example, R(–) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(–) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(–) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(–) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(–) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(–) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(–) albuterol. The two (or more)

drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalant form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

Equivalents

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of inducing bronchodilation or providing relief of bronchospasm, comprising administering to an individual a quantity of optically pure R-(−) albuterol sufficient to induce said bronchodilation.

2. A method according to claim 1, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

3. A method according to claim 1, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim 1, wherein the optically pure R(−) albuterol is administered by inhalation.

5. A method according to claim 4, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

6. A method according to claim 1, wherein the optically pure R(−) albuterol is administered orally.

7. A method according to claim 6, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

8. A method according to claim 6, wherein the optically pure R(−) albuterol is administered as a syrup.

9. A method according to claim 7, wherein the optically pure R(−) albuterol is administered as a syrup.

10. A method of inducing bronchodilation or providing relief of bronchospasm while reducing the concomitant liability of adverse effects associated with racemic albuterol, comprising administering to an individual a quantity of optically pure R-(−) albuterol sufficient to induce said bronchodilation while simultaneously reducing said adverse effects.

EXHIBIT 9

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United States Patent and Trademark Office

July 27, 2006

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U.S. PATENT: *6,083,993*

ISSUE DATE: *July 04, 2000*

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W. MONTGOMERY

Certifying Officer

US006083993A

United States Patent [19]

Barberich et al.

[11] Patent Number: 6,083,993

[45] Date of Patent: *Jul. 4, 2000

[54] METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R(–) ALBUTEROL

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor Inc., Marlborough, Mass.

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: 09/466,107

[22] Filed: Dec. 17, 1999

Related U.S. Application Data

[63] Continuation of application No. 09/200,541, Nov. 25, 1998, which is a continuation of application No. 09/063,551, Apr. 21, 1998, Pat. No. 5,844,002, which is a continuation of application No. 08/691,604, Aug. 15, 1996, Pat. No. 5,760,090, which is a continuation of application No. 08/335,480, Nov. 7, 1994, Pat. No. 5,547,994, which is a continuation of application No. 08/163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of application No. 07/896,725, Jun. 9, 1992, abandoned, which is a continuation of application No. 07/461,282, Jan. 5, 1990, abandoned.

[51] Int. Cl.[7] A61K 31/135

[52] U.S. Cl. 514/649

[58] Field of Search 514/649

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Muittari et al. "Comparison of acute bronchodilator effects of oral salbutamol, . . . " *Chem. Abstr. 89*: 123259m (1978).

Primary Examiner—Raymond Henley, III
Attorney, Agent, or Firm—Hesslin & Rothenberg, P.C.

[57] ABSTRACT

The optically pure R(–) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(–) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

17 Claims, No Drawings

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CROSS REFERENCE TO RELATED APPLICATIONS

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The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(-) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(-) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs.

In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(-) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(-) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(-) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^3[(tert-butylamino) methyl]-4-hydroxy-mxylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(-) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(-) isomer of albuterol is administered to an individual who has asthma. For example, R(-) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(-) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(-) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(-) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(-) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(-) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine

or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalant form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

What is claimed is:

1. A method of treating bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(−) albuterol.

2. A method according to claim 1, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

3. A method according to claim 1, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim 1, wherein the optically pure R(−) albuterol is administered by inhalation.

5. A method according to claim 4, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

6. A method according to claim 1, wherein the optically pure R(−) albuterol is administered orally.

7. A method according to claim 6, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

8. A method according to claim 6, wherein the optically pure R(−) albuterol is administered as a tablet, capsule or syrup.

9. A method according to claim 7, wherein the optically pure R(−) albuterol is administered as a syrup.

10. A method of preventing bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(−) albuterol.

11. A method according to claim 10, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

12. A method according to claim 10, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

13. A method according to claim 10, wherein the optically pure R(−) albuterol is administered by inhalation.

14. A method according to claim 13, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

15. A method according to claim 10, wherein the optically pure R(−) albuterol is administered orally.

16. A method according to claim 15, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

17. A method according to claim 15, wherein the optically pure R(−) albuterol is administered as a tablet, capsule or syrup.

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